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Clinical Proceedings

OF THE

CHILDREN'S HOSPITAL

WASHINGTON, D. C.

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Ulcerative Colitis in Infancy

DONALD W. WICZER, M.D.*

Although chronic ulcerative colitis in childhood is well known,[1-9] its relative infrequency in infancy has led to the presentation of the following case report and a discussion of the general pediatric aspects of this disease.

CASE REPORT

First Admission:

This white male infant was first admitted to Children's Hospital June 26, 1958 at the age of 10 months for investigation of bloody diarrhea and vomiting. The vomiting was intermittent in nature and followed the addition of solid foods to the diet beginning five months earlier. Cereals and bananas were particular offenders. Two months prior to admission the infant began having bouts of intermittent diarrhea following the administration of solid food. The stools at the onset of diarrhea would change color from yellow to green; bright red blood and mucus were seen on many occasions. No fever, obvious discomfort, tenesmus, anorexia, or skin eruptions were reported. The stools occurred almost exclusively during the daytime, and increased in frequency to four to five bowel movements a day. The vomiting subsequently decreased in frequency and eventually ceased. The infant had no siblings; his parents were well. He was the product of a normal pregnancy and delivery, and weighed 7 pounds at birth. He was said to have been slightly jaundiced for the first six to seven days of life, but required no blood transfusions. He was breast fed until 4 months of age at which time Similac® was started and continued until admission. Cereals were started at 4½ months but led to the aforementioned episodes of vomiting and diarrhea. Meats, vegetables, fruits, orange juice, iron and vitamins were all added to his diet in the fifth through eighth months of life. He began teething at 6 months and sat alone at 10 months. Except for the bowel complaints the child had been perfectly well, had none of the common childhood illnesses and had been started on the routine immunizations.

Physical examination on admission revealed a well developed, well nourished white male infant in no acute distress, lying quietly in bed except for occasional short outbursts of crying. His color was normal. His rectal temperature was normal, his pulse rate was 128 and his respirations were 20 per minute. His weight was 16 pounds 12 ounces. His head measured 17½ and his chest 18 inches in circumference. The skin was normal; there was minimal generalized lymphadenopathy. The tympanic membranes were somewhat injected. Four upper and two lower incisors were present. The gums and mucous membranes were pale. The remainder of the physical examination was normal.

Admission urinalysis was normal. Blood hemoglobin was 11.5 Gm. per 100 ml., hematocrit 35 per cent, white blood count 19,700 per cu. mm. with 41 per cent segmented neutrophils, 56 per cent mature lymphocytes, 1 per cent basophils, and 2 per cent monocytes. Blood cultures were negative. Repeated stool cultures and examinations for ova and parasites, including examination of direct specimens taken

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during a proctoscopic procedure, failed to reveal any causative organisms. The serum contained no agglutinins for salmonella, brucella or proteus antigens. Fasting blood glucose level was normal. The concentration of chloride in the sweat was 24.8 mEq. per liter. Studies of the blood coagulation including platelet count, prothrombin time, and prothrombin consumption, and bleeding and coagulation times revealed no abnormalities. Stool eosinophils and eosinophil counts of the peripheral blood prior to, and 20 to 45 minutes after, ingestion of wheat cereals showed no significant changes. Histoplasmin and tuberculin skin tests were negative. An upper and lower gastrointestinal series of x-rays with barium were normal. Proctoscopic examination revealed edematous mucosa containing several hemorrhagic spots. No ulcerations were noted. The mucosa bled on contact with the proctoscope. Skin testing showed a positive reaction to wheat, oats and eggs.

While in the hospital the infant spiked a low to moderate grade fever on several occasions. He averaged three diarrheal stools daily; these often contained blood and mucus. Initially following admission he was given Hi-Pro,® clear liquids, iron and vitamins. Procaine penicillin was administered for the otitis media. On July 14, weighing 17 pounds 4 ounces, he was discharged from the hospital, to be fed a hypoallergic diet and to be followed closely in the allergy clinic.

Second Admission:

The infant was again admitted to Children's Hospital December 8, 1958 at the age of 16 months because of continued loose stools often containing blood and mucus, and usually totaling 5 to 10 movements daily. In the interim he had been given a meat base formula, and for the month prior to admission skim milk. He had also been followed in the hematology clinic where intramuscular iron was administered for an iron deficiency anemia which had developed since the previous admission. On December 4, x-ray studies of the wrist had shown a bone age of approximately 9 months. At that time, a barium enema had revealed the large bowel to be somewhat rigid and showing a lack of haustral markings throughout its entire length, suggesting ulcerative colitis.

On admission physical examination the infant appeared somewhat undernourished and irritable but in no acute distress. He rocked his entire body from side to side and sucked his thumb. His temperature was 99.4°F. The pulse was 90 and the respirations 22 per minute. His weight was 18 pounds 3 ounces. His head and chest circumferences measured 18 inches each. A few excoriations were present over the face and legs. Minimal lymphadenopathy was present in the cervical and inguinal regions. The anterior fontanel measured 1.5 cm. Eight incisors were present and four molars were erupting. The tonsils were moderately enlarged but not injected. The heart and lungs were normal. The abdomen was scaphoid but no masses or organs were palpable. The extremities appeared somewhat wasted and a general flaccidity prevailed. The deep tendon reflexes were hypoactive. No pathological reflexes were present.

Urinalysis was again normal. Blood hemoglobin was 10.1 Gm. per 100 ml., hematocrit 38 per cent, white blood count 31,300 per cu. mm. with 71 per cent segmented neutrophils, 26 per cent mature lymphocytes, and 3 per cent monocytes. The prothrombin activity was 13 per cent but improved to 77 per cent after vitamin K_1 oxide was administered. All stool cultures for pathogenic bacteria were negative, and studies of fresh stool specimens for ova and parasites were unrevealing. The blood ascorbic acid was 2.25 mg. per 100 ml. The protein bound iodine was 4.1 mcgm. per 100 ml. The blood urea nitrogen was 11 mg. per 100 ml. Electrolyte studies including calcium and phosphorus were reported as normal. Barium enema one week following

readmission was again suggestive of ulcerative colitis. Generalized osteoporosis was noted to be present. Sigmoidoscopy revealed a large amount of mucus in the intestinal lumen and easy bleeding of the mucosa. The impression was ulcerative colitis.

Therapy consisted of a high calorie, high protein, low residue diet. Multivitamins, including high doses of vitamins C, K, and D, were given. Iron, antispasmodics, antihistamines and sulfonamides with the addition of a broad spectrum antibiotic during febrile episodes were also employed in his therapy. HP-ACTHAR Gel was started on April 1. The dosage varied from 40 to 80 units intramuscularly every other day. The child seemed to improve somewhat with the addition of the ACTH in that his stools became less frequent, and when ACTH was reduced below 35 units every other day his condition deteriorated.

The child would not sit alone on admission but after six months of hospitalization could speak a few words, walk with support and take a few steps alone. He was still having an average of four to five stools daily, many of which contained blood in small amounts. His weight was 22 pounds on June 10 when he was discharged to a convalescent home. The ACTH was to be continued there at the dosage of 40 units every other day. The child seemed to make excellent gains psychologically, and intensive psychological and psychiatric study continues.

DISCUSSION

According to Valdes-Dapena,[10] ulcerative colitis was first described in its classical form by White in 1888, and 117 cases were reported by Logan in 1919; the first reference to chronic ulcerative colitis in children was made by Helmholz in 1923 when he reported 5 cases ranging from 2½ to 10 years of age. Chronic ulcerative colitis in infancy has been reported infrequently. Valdes-Dapena was able to find 29 cases of ulcerative colitis in infants in the literature, with ages ranging from birth to 18 months, and reported on a case of fulminant ulcerative colitis in a newborn with symptoms beginning a few days after birth. X-rays demonstrated typical changes from the mid transverse colon to the rectum, and postmortem examination showed ulceration from the ileocecal valve extending to the anus. Vedel-Jensen[11] reported a case in a 3 day old infant with constant diarrhea and vomiting. The diagnosis was confirmed at autopsy, both grossly and microscopically. Beranbaum and Waldron[12] reported a case of chronic ulcerative colitis in a child whose first symptom occurred at the age of 21 days. Quaiser[13] reported 85 infants, all aged 1 to 3 months, with what he calls enterocolitis ulcerosa necroticans; postmortem examination in these cases demonstrated extensive changes in the neighborhood of the ileocecal valve. Bacteriologic and parasitologic as well as viral studies failed to reveal a causative pathogen.

The etiology of chronic ulcerative colitis remains obscure. Allergy or hypersensitivity to food as an etiologic or contributory agent in the disease has been suggested, with the offending food frequently one in common use. With the use of elimination diets, certain foods may be demonstrated to cause recrudescence of symptoms.[9] The patient presented in this report

was allergic to cereals and eggs. It has been stressed that particular attention be paid to food idiosyncrasies or sensitivities in ulcerative colitis.[14] Schreiner and associates[8] report a case of ulcerative colitis in a 4 year old girl with possible food allergy, but state that usually the entire gastrointestinal tract is involved and the changes are not confined to the colon.

Despite the unknown etiology of ulcerative colitis, many authors emphasize the role of emotional disturbances.[1, 6, 7, 9] Wright and Kenwood[15] report a boy followed for 15 years with ulcerative colitis which started at 27 months of age, and they stress the psychiatric aspects of the case. Schreiner and associates,[8] in their case report, emphasize psychiatric study and therapy in this syndrome. Symptoms of patients with this illness very often coincide with periods of emotional upheaval. It is often difficult to determine whether the psychiatric state of a person with chronic ulcerative colitis is a cause or a result of the colitis.

The presence of excess lysozyme in this disease has frequently been mentioned in the past but it has never been clear what part this plays.

Ulcerative colitis classically presents as a watery diarrhea with blood and mucus in the stools. Fever often ushers in the attack and a leukocytosis may be present. Gastroenteritis is often considered in the differential diagnosis. Relapses occur often during the months when upper respiratory infections are prevalent, and upper respiratory infections often usher in the illness.[4] Serious electrolyte derangement, anemia, malnutrition, and failure in normal growth and development may ensue.

Inflammatory changes in the large bowel usually begin in the rectum and progress toward the cecum. Right-sided colitis and universal colitis are less common. The colon shows all grades of inflammation from edema, congestion and redness of the mucosa, which bleeds easily, to superficial and deep ulceration. At a later stage in the illness patches of undestroyed mucosa or pseudopolyps are seen. Huge sloughing secondary ulcers and, at times, perirectal abscesses and fistulas are found. With chronicity, the bowel shortens due to scarring and fibrosis and is converted into a rigid, infected tube.

The diagnosis in a patient with the symptoms of watery, bloody diarrhea, and in whom bacteriologic and parasitologic studies fail to reveal a pathogen, is based on sigmoidoscopic and barium enema x-ray studies showing the typical changes. X-ray of the colon, with barium instilled, frequently shows lack of haustral markings, serrated mucosa, narrowing of the lumen and shortening of the bowel. Sigmoidoscopic findings generally precede x-ray changes; however, in the case reported by Schreiner and associates[8] only the x-ray findings were abnormal.

Medical management starts with hospitalization in the acute stage

because a change in environment will often contribute to the relief of symptoms. Restoring fluid and electrolyte balance by appropriate fluids is important. The diet must supply the necessary calories, proteins, fats and minerals, and during exacerbations a low residue diet is preferred. High doses of vitamins are recommended. Transfusions of whole blood may at times be necessary. In the anxious patient sedative drugs are helpful. The use of antispasmodics to help correct the disturbed physiology of the gastrointestinal tract has been helpful. The use of a bowel sterilizer, usually a sulfonamide, to control the ever-present, but seldom bacteriologically identified, low grade infection in the involved colon is well accepted. Salicylazosulfapyridine (Azulfidine®), which was employed in our case, has found many advocates.[4] During an acute attack a broad spectrum antibiotic is added. It is important that chemotherapy be administered as early as possible during the course of the disease and be continued for a long period of time following the attack. Soothing solutions and suspensions, such as kaolin and warm oil, are sometimes instilled into the rectum to lessen tenesmus and anal pain.[6]

The use of ACTH, cortisone, hydrocortisone and their analogues has been advocated by many. They find the best use of these substances in patients with disease of short duration and minimal bowel change but with marked symptoms.[9] According to Kiefer and associates,[14] "As the cases become more and more complicated with secondary infections and organic changes the value of steroids decreases." They caution against the use of steroids in severely septic patients in whom other complications may be obscured and advise waiting for the temperature to return to normal before using these hormones. Electrolyte disturbances, spontaneous perforation of the bowel, and other serious complications may follow the use of steroids. Many find that the use of ACTH and steroids gives generally poor results and comment that they are of little use in this disease in the pediatric age group.[4,7] Our use of ACTH in the infant reported seemed to have a moderately beneficial effect on his condition.

Psychotherapy is considered by all to be of importance in the treatment and care of the ulcerative colitis patient.

There are wide differences of opinion on the indications for surgery in ulcerative colitis. In the pediatric age group the performance of ileostomy for any cause is recommended with great reluctance. Chronic resistant cases and those developing strictures, fistulas, perforation, secondary polyposis, uncontrolled bleeding and perirectal abscess are generally treated surgically. Those patients threatened with such serious sequelae as arthritis, severe growth failure and malignant degeneration, impending or actual, are also candidates for surgery. It is said that 8 to 10 per cent of carcinoma

of the large bowel arises in ulcerative colitis; this is usually found in cases of over 10 years duration.[14] The development of cancer in chronic ulcerative colitis is said to be rare in children under 16 years of age; according to Wilcox and Beattie[16] only 5 such cases were reported in the literature prior to 1956. Of the 25 infants and children with ulcerative colitis described by Meeker and Goff,[7] four had surgery performed; one who had simple ileostomy died of cancer of the colon eight years later. Holowach and Thurston[2] reported colonic carcinoma in 2 of 18 children with chronic ulcerative colitis. Perhaps the most important indication for surgery, as suggested by Cattrell,[14] is when the patient, with frequent hospitalizations, becomes such an economic and emotional problem to himself and his relatives that life is unendurable. The type of surgery performed depends on the experience of the surgeon and the physical condition of the patient. With adequate medical management, the frequency of performance of emergency surgery for this condition has decreased. Ileostomy with total colectomy in a one or two stage procedure, with or without an abdominal-perineal resection of the rectum, is generally agreed upon as being the best procedure available. Simple ileostomy does not necessarily control bleeding nor does it remove the site of possible later malignancy. Anastomosis of the ileum to the rectum has been tried in England and results seem satisfactory, but there has been little experience with this procedure in the United States.[14] The routine care of the ileostomy and emotional support of the patient by such organizations as the QT Alumni are discussed elsewhere.[6, 7]

Complications of the disease such as polyposis, erythema nodosum, splenomegaly, phlebitis, nephritis and endocarditis should be mentioned. Lagercrantz[5] reported thrombosis and liver damage in one third of his 134 cases of ulcerative colitis in children. The clinical relationship of ulcerative colitis to the systemic collagen diseases such as rheumatoid arthritis and disseminated lupus erythematosis is suggested by Wallgren.[3] The unusual problem of amyloidosis with adrenal insufficiency occurred in one patient described by Kirsner's group.[1] The retardation of growth and development in patients with chronic ulcerative colitis should be stressed, particularly when the disease is active during the physiologic growth periods of infancy and adolescence, as demonstrated in the present case.

SUMMARY

A case of chronic ulcerative colitis beginning at the age of 8 months is reported. A brief discussion of chronic ulcerative colitis in the pediatric age group including the diagnosis and management is presented. The combined efforts of the pediatrician, psychiatrist and surgeon are invaluable in the treatment of this illness in the pediatric age group.

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Acute Ferrous Sulfate Poisoning in Children; Report of Five Cases

George C. Emmanouilides, M.D.*

The medical profession is becoming more and more aware of the fact that iron preparations are not inocuous medications. They may produce severe, and in many instances fatal, poisoning when accidentally ingested by the inquisitive toddler.

* Research Fellow in Hematology, Children's Hospital.

Although iron preparations have been present for many centuries in the medical armamentarium it is strange that the report of iron toxicity which initiated the current interest appeared as late as 1947, when Forbes[1] reported two fatal cases from England. Since then quite a number of reports have appeared in the English and American literature,[2-24] thus supporting the fact that iron poisoning is not an uncommon occurrence in late infancy and early childhood. The importance and the seriousness of this condition have been emphasized, as well as the recommendation that iron preparations should no longer be considered nontoxic, and several suggestions regarding the pathogenesis and treatment have been made.

Acute ferrous sulfate poisoning has been observed in five instances within a period of less than six months at Children's Hospital. One patient died, one was severely affected, and three were mildly affected. Clinical and laboratory observations with a brief discussion are presented in this report.

CASE REPORTS

Case 1.

B. C., an 18 month old Negro girl, was brought to the outpatient department at 5:00 P.M., September 19, 1958 approximately two hours after ingesting 20 to 25 tablets of ferrous sulfate (3 grains each). One hour after ingestion the child vomited a brownish fluid which contained a few red strands of blood. The mother noticed a few scattered "pills" on the floor and immediately brought the child to the hospital. The child was alert on arrival and gastric lavage was performed. Toward the end of the procedure she became lethargic for the first time.

Physical examination at that time revealed a well developed and well nourished semicomatose child. She responded only sluggishly to painful stimuli. Her respirations were deep and regular. Her pulse was 130 per minute and her blood pressure 90/50. Her eyes were moderately sunken and the pupils reacted sluggishly to light. The corneal reflexes were absent and there was slight cyanosis of the lips. The deep tendon reflexes were decreased. During the initial examination she twice vomited a brown watery vomitus which contained a small amount of bloody mucoid substance. Laboratory data are summarized in table 1.

She remained in deep coma until about 9:00 P.M. when for the first time she cried during a venous puncture. Meanwhile her blood pressure dropped to 70/30 and 100 ml. of whole blood was administered and was followed by continuous intravenous infusion of fluids. Fifty milligrams of vitamin K (Mephyton®) was given intravenously. Her pulse and blood pressure remained stable, but she continued to be lethargic. At midnight she was more responsive and rather irritable. Two loose greenish black stools were reported. The following morning she was more alert and breathing normally. Moderate acidosis developed subsequently and was corrected with intravenous fluids. She was again given 125 ml. of whole blood because of a falling hemoglobin (from 10.0 to 8.8 Gm. per 100 ml.). On the second hospital day her condition improved remarkably and she was discharged eight days later in satisfactory condition. On March 19 an x-ray examination of the upper gastrointestinal tract showed no evidence of obstruction.

Case 2.

D. W., a 3 year old white girl, was brought to the hospital October 8, 1958 with a history of having eaten "iron pills" of unknown quantity approximately one hour

TABLE 1

Laboratory Data of Case 1

Date and Time	9-19-58 6:30 P.M.	9:30 P.M.	12:00 P.M.	9-20-58 9:00 A.M.	3:00 P.M.	9-21	9-22	9-23	9-26	9-27
Serum iron (mcgm/100 ml)	3194	2000	1277	736	513		222		125	
Prothrombin activity (% of normal)		27.0			45.0	56.0			23	94
Leukocyte count		32,200			16,400			9,100		
Sodium (mEq/L)		138.0			120.0	135.0				
Potassium (mEq/L)		3.5			3.4	4.5				
Chlorides (mEq/L)		111.0			94.0	106.0				
CO_2 (mEq/L)		14.1			10.0	16.8				
Total bilirubin (mg/100 ml)							2			1
Cephalin flocculation							1+			1+

previously. Following the ingestion she had vomited a greenish brown watery material three times. No diarrhea was noted. On physical examination she was found to be well developed and well nourished and rather pale. Her respirations were normal. Her pulse was 140 per minute and her blood pressure 125/75. Yellowish green discoloration of the teeth was noted. The remainder of the examination was not remarkable. Gastric lavage was performed but no evidence of ingested tablets was found. During the two hours following admission she became slightly lethargic and her blood pressure fell to 80/60. She was treated with intravenous fluids. The only abnormal laboratory finding was an elevated serum iron, 597 mcgm. per 100 ml., two and one-half hours after the ingestion of the tablets. She was discharged two days later in satisfactory condition.

Case 3.

C. H., a 2 year old Negro girl, was brought to the emergency room November 24, 1958 with a history of swallowing an unknown quantity of "iron pills" two hours earlier. The tablets had been given to her post-partum mother a few days previously. While at home the patient had vomited four times, but no diarrhea had been noted. Upon arrival she was found to be alert and rather irritable. Her pulse was 135 per minute and her respirations were normal. Her blood pressure was 100/68. The remainder of the physical examination was not remarkable. Gastric lavage was performed with 400 cc. of mild bicarbonate solution. The only abnormal laboratory finding was an elevated serum iron of 639 mcgm. per 100 ml. which the following day was reported as being 472 mcgm. per 100 ml. She had an uneventful hospital course and was discharged two days after admission.

Case 4.

W. T., an 18 month old Negro girl, was in good health until midnight of December 22, 1958 when she developed persistent vomiting and watery diarrhea. Approximately 18 to 20 tablets were seen in her vomitus. Her mother recognized them as some given to her a few weeks previously at the time of a post-partum check-up. The exact number of ingested tablets was not known. The vomiting and diarrhea continued for about two hours. The patient subsequently became comatose and remained in this state for about six hours. The mother thought that the child was "sleeping." About 30 minutes prior to arrival at the hospital, the patient awoke and began

to cry. This was soon followed by coma, and the patient was rushed to the hospital. Upon arrival she was found to be in a deep coma with slow, superficial and irregular respirations. The pulse was very weak and irregular, and no blood pressure could be detected. She was pronounced dead a few minutes later before treatment could be instituted. Autopsy results are not available.

Case 5.

On February 17, 1959 C. E., a 3 year old Negro boy, swallowed an unknown number of ferrous sulfate tablets and subsequently developed vomiting. The vomitus contained chewed-up tablets with white particles in it. He became very thirsty and refused his supper. Three hours later he vomited again and had a loose watery stool. He was brought to the hospital and a gastric lavage was perfomed. On physical examination he was alert and irritable. His respirations, pulse and blood pressure were normal. His tongue was brownish in color. A few impetiginous lesions were present over both extremities. The neurological examination was not remarkable. His serum iron level on admission was 766 mcgm. per 100 ml. The other laboratory examinations performed were within normal limits. His hospital course was uneventful. He was treated with intravenous fluids and was discharged after two days in good condition.

DISCUSSION

In a review of 42 case reports of iron poisoning from the medical literature, Aldrich,[21] in 1957, noted that approximately 50 per cent of the reported cases were fatal. It is apparent that many more instances of acute iron poisoning occur, since mild cases usually are not being reported and other moderately severe cases are overlooked. The fact that our cases have occurred during a period of less than six months supports the above statement. In all our cases the iron was taken accidentally in the form of 3-grain ferrous sulfate tablets. This medication had been given to adults for treatment of anemia (in four instances to the mother, prenatally or postnatally). Cases 2, 3 and 5 were mild, the main symptom being vomiting. Diarrhea and lethargy of short duration were noted in one case. All 3 of these patients had an uneventful recovery and were discharged on the third hospital day. The only abnormal laboratory finding in these 3 children was an elevation of the serum iron which ranged between 597 and 766 mcgm. per 100 ml. (the normal serum level of iron is 125 to 175 mcgm. per 100 ml.). All blood samples were obtained approximately two and one-half to three and one-half hours after ingestion of the tablets. We believe that if proper facilities are available, a serum iron determination is the best laboratory test for confirming the diagnosis and detecting the severity of the poisoning.

Case 1 represents a rather severe case of iron poisoning, and resembles in its clinical picture most of the previously reported cases.

Acute iron poisoning can be divided clinically into four chronological phases.[2, 10, 21] The first phase is characterized by vomiting, diarrhea and, subsequently, symptoms of cardiovascular collapse, lethargy and coma. It lasts approximately six to eight hours. One fifth of the fatal cases occur

in this phase. The second phase is characterized by a temporary improvement of the patient and lasts 10 to 16 hours. This phase is very important because at any time a sudden relapse of a severe and usually irreversible cardiovascular shock may occur. The latter represents the third phase and may occur 20 to 56 hours after ingestion of the poison. Seventy-five per cent of the fatal cases usually succumb during this phase. The last phase occurs as a very late manifestation of this clinical syndrome in those patients who recover from the more severe form. Signs and symptoms of gastrointestinal obstruction, secondary to scarring, may appear one month or more later. Surgical intervention is necessary when this complication occurs.[16, 19, 23]

The age incidence of our cases was between 18 and 36 months, similar to those observed in other reports.[2, 10, 21] All cases were from the lowest socio-economic class, and there were four Negroes and one white. It was not possible to determine the exact dosage of the ingested tablets except in case 1. The fatal dosage varies widely. Spencer[10] reported fatal poisoning with 4.8 Gm. of ferrous sulfate, while recovery has followed ingestion of 15 Gm.[10, 14] It is apparent that factors such as fullness or emptiness of the stomach before the ingestion, or vomiting which occurs soon after, may bear a relationship to the severity of the poisoning.

Pathologic findings include necrotizing gastritis, and congestion and ulceration of the mucosa of the stomach or small intestine.[8, 17, 20, 22] Mesenteric lymphadenitis and thrombosis of the mesenteric veins may occur.[13] Cloudy swelling and periportal hemorrhagic necrosis of the liver and other viscera have been observed.[17]

In individuals suffering from acute iron poisoning, very high plasma iron levels have been demonstrated together with a marked leukocytosis, increased serum bilirubin and decreased carbon dioxide combining power. Decreased prothrombin activity was observed in case 1 and a similar finding has been observed by others.[5] There have been no reports of blood coagulation abnormalities among the survivors.[33]

There is a suggestion that some correlation between the serum iron level and the severity of the poisoning exists. Serial examination of serum iron in case 1 showed results similar to those observed by others (see tables 2 and 3). In 7 cases of iron intoxication reported in the literature serum iron determinations were performed. A level as high as 8,150 mcgm. per 100 ml. of serum iron has been observed in a patient who survived.[5] The lowest reported iron level was 1,680 mcgm. per 100 ml.[24] In this case drowsiness and lethargy were observed. There have been no reports of serum iron levels in fatal cases. In case 1 the highest level observed was 3,194 mcgm. per 100 ml.; three hours later this had dropped to 2,000 mcgm. per 100 ml. At this time, when the blood sample was taken, the child began to respond

TABLE 2

Serum Iron Levels Correlated with Clinical Findings as Recorded from the Literature

Author	Amount Ingested	Initial Serum Iron	Coma	Drowsiness	Outcome	Serum Iron after 24 Hours
	Gm.	*mcgm/100 ml*				*mcgm/100 ml*
Spencer[10]	15	3,300	+		Recovered	1,120
	6	3,420	+		Recovered	330
Kaplan et al.[21]	6	1,680		+	Recovered	normal
Birk et al.[7]	13	4,000	+		Recovered	2,000
Brown and Gray[24]	8	5,450	+		Recovered	450 (42 hours)
Davis and Gibbs[5]	?	8,120	+		Recovered	
Amerman et al.[9]	4	3,500	+		Recovered	

TABLE 3

Serum Iron Levels Correlated with Clinical Findings in Four Cases of Iron Intoxication Seen at Children's Hospital

Case No.	Age	Initial Serum Iron	Serum Iron after 24 Hours	Vomiting	Diarrhea	Drowsiness	Coma
	months	*mcgm/100 ml*					
1. (B. C.)	18	3,194	513	+	+		+
2. (D. W.)	36	597	139	+	+	+	
3. (C. H.)	24	639	472	+			
5. (C. E.)	36	766		+			

to stimuli and cried. Subsequent determinations showed a steady decline, while the general condition of the patient steadily improved. On the third hospital day the serum iron was within normal limits. From the above observations there is some evidence that high serum iron levels are associated with coma during the first phase. There appears to be a wide variation in the serum iron levels associated with central nervous system depression. The latter usually is seen with iron levels over 2,000 mcgm. per 100 ml.

The exact mechanism of death during the first phase is not known. Large amounts of ferritin are released from the gastrointestinal tract into the blood due to the local effects of iron.[15, 22, 27] As ferritin is a potent vasodepressor, absorption of large amounts could explain the shock observed in this phase.[28] Brown and Gray[24] postulated that a direct toxic action of uncombined iron also exists during this phase. The mechanism of death during the third phase is attributed to severe liver damage.

There is no specific treatment for this poisoning. General supportive measures have been recommended. Emptying the stomach by induction of

vomiting or gastric lavage and the use of whole blood, plasma or plasma substitutes as supportive measures to overcome the shock are the main steps in treatment. Correction of the electrolyte imbalance with proper intravenous fluids is necessary. Our case 1 was treated only by supportive measures and the child had an uneventful recovery. The use of BAL is controversial.[31] The use of the artificial kidney has been suggested but it is important to consider the fact that a large part of the iron in the serum remains in the ferric state and cannot be dialyzed.[29, 30] Chelating agents have been used but no published reports are available as yet.[21] Exchange blood transfusion was recently performed in one case with apparently good results.[9] We believe that exchange transfusion carefully performed within the first six hours after the ingestion of the iron may greatly benefit the severely poisoned child.

As in any accidental poisoning of early childhood, the most important responsibility for prevention lies with the parents. They should be warned that "iron pills" are dangerous for children and should be carefully locked up in an inaccessible place. The physician and the pharmacist should realize the hazard of prescribing large numbers of tablets to pregnant women or to blood-bank donors. In contrast, small numbers of tablets packaged in tight wrappings should be delivered to the iron-deficient adult. In four of our cases an uncounted number of "iron tablets" were given to the mother by an obstetrical outpatient clinic.

SUMMARY

Five cases of acute accidental ferrous sulfate poisoning are reported. Three of them were mild, one severe, and one fatal. The incidence of this poisoning is not uncommon. Serial determinations of the serum iron in the severe case were performed, and the observations made are recorded. The clinical picture, pathological findings, pathogenesis, treatment and prevention of this syndrome, with a brief review of the English literature, are discussed. We believe that treatment with exchange transfusion during the first four to six hours may greatly benefit the severely poisoned child.

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Salmonella Osteomyelitis Complicating Sickle-Cell Anemia

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Although the first case report of coincident Salmonella osteomyelitis and sickle-cell anemia may have been that of Carrington and Davison[1] in 1925, better documented cases have subsequently been reported in more recent literature.[2-16] Diggs, Pulliam and King[2] drew attention to the fact that bone and joint infections are more common in patients with sickle-cell anemia than they are in normal individuals. The following case illustrates the fact that Salmonella osteomyelitis is a complication which must be considered in any case of sickle-cell disease presenting with bony involvement. As will be discussed later, predisposition to this infection is probably encouraged by previous tissue damage characteristic of sickle-cell disease.

CASE REPORT

The patient, a 5 year old Negro girl, was admitted to Children's Hospital September 25, 1958 with the chief complaint of swelling of her hands and feet. A diagnosis of sickle-cell anemia was first made in 1954. She had had two subsequent hospital admissions, at which time diagnoses of sickle-cell anemia in crises were made.

The patient had had swelling of her hands for five days and swelling of her feet for three days prior to admission. She had developed large bullae filled with clear fluid on her feet on the day before she entered the hospital. Progressive abdominal swelling occurred five days prior to admission, and rapid respirations one day prior to admission. Her urine had been noted to be dark for five days.

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On physical examination at the time of admission to the hospital the positive findings included: increased A-P diameter of the chest, hyperresonance of the lung fields, mild cardiomegaly, sinus tachycardia, a harsh systolic murmur at the apex, abdominal distention, hepatomegaly and atrophic skeletal musculature. There was swelling over the dorsal surface of the base of the left thumb and forefinger. Swelling also extended over the entire dorsum of the right hand. The overlying skin was tense and partly fluctuant.

There was a bilateral marked swelling at the base of the great and second toes. There was purulent material exuding from a bullous lesion on the left foot and seropurulent material was draining from a lesion on the right foot.

Laboratory examination on admission revealed a hemoglobin of 7 Gm. per 100 ml., an hematocrit of 28 per cent and a white blood cell count of 34,200 per cu. mm., of which 74 per cent were polymorphonuclear neutrophiles. Urinalysis was normal. A sickle-cell preparation demonstrated 80 per cent sickling. Electrophoretic study of the hemoglobin showed an SS pattern.

Four blood cultures did not grow any organisms, but cultures of lesions on the left hand and right foot obtained the day after admission grew out Salmonella Group B. Stool cultures obtained October 13 and 21 also grew Salmonella Group B.

Serological studies showed the following results:

	10-21-58	11-10-58
	Titers	
Typhoid H	Negative	1:80
Salmonella		
Group A	Negative	1:20
Group B	1:320	1:320
Group C	1:80	1:320
Group D	1:160	1:60
Group E	1:80	1:80
Paratyphoid		
Group A	Negative	1:80
Group B	1:160	1:20
Group C	Negative	1:60

Initial x-ray examination of the upper extremities showed soft tissue swelling over the thenar areas. There was generalized osteoporosis of all the bony structures. Definite bone destruction was present throughout the shaft of the second metacarpal of the left hand. A periosteal reaction was noted in the distal diaphysis of the right radius. Repeat x-rays taken two weeks later showed a decrease in the soft tissue swelling. There had been a progression in the destruction of the second left metacarpal and there was noted a periosteal reaction about the shaft of the second right metacarpal; this metacarpal also showed increased bone density (fig. 1A). Three weeks after initial x-rays were taken, there was some healing of the second left metacarpal, while destruction was more marked in the second right metacarpal. At this time a circumscribed area of bone destruction was noted in the distal shaft of the right radius. Severe destruction of the shaft had occurred in the first and fourth metatarsals of the right foot and the first metatarsal of the left foot (fig. 1B).

The patient was kept at bed rest throughout the hospital stay. Initially, penicillin

FIG. 1A. Roentgenographic views of both hands showing bony destruction of the shaft of the second left metacarpal bone; there is also increased density of the second right metacarpal bone and a periosteal reaction of the shaft.

and tetracycline were given, but the therapy was changed to chloramphenicol, 2 Gm. daily by mouth, on the second hospital day and continued for 11 days when vomiting prohibited the oral route. Lesions on the feet and left hand were debrided on the day of admission. Two transfusions of packed cells were given because of a drop of hemoglobin to 5.6 Gm. per 100 ml.

By the twentieth hospital day, both hands were externally healed and were nontender; there was, however, limitation of flexion of both second metacarpal-phalangeal joints. At this time, there was still slight drainage from the medial aspect of the first metatarsal bilaterally. Since cultures of this material revealed hemolytic *Staphylococcus aureus* sensitive only to kanamycin, therapy with this drug was instituted and continued until the forty-second hospital day.

On October 21 the patient was started on treatment with anti-typhoid-paratyphoid A, B, and C vaccine which was given in ½ ml. amounts subcutaneously every four days for four doses. Gamma globulin, 5 ml. subcutaneously, was also given at one to two day intervals for five doses. Both of the above medications were given in an attempt to eradicate Salmonella from both the bones and the stools. Chloramphenicol was continued until the forty-third hospital day.

On three subsequent admissions, repeated blood and stool cultures have remained negative. In January 1959 x-rays of the feet revealed generalized osteoporosis. The previously reported changes in the metatarsals had undergone some healing. The patient has continued to receive physical therapy on an outpatient basis, is now ambulatory and has fairly normal use of her hands.

FIG. 1B. Roentgenographic views of both feet showing destructive changes in the first and fourth right metatarsal (right) and the first left metatarsal bones (left).

DISCUSSION

Osteomyelitis is a rare complication of salmonellosis in the normal individual. In an analysis of nearly 8,000 human infections, Saphra and Winter[17] noted osteomyelitis occurring in less than 1 per cent. A much higher incidence of osteomyelitis occurring in *S. choleraesuis* infection has been reported in several smaller series.[18, 19]

Diggs's group[2] has pointed out that the pathologic changes in bone in sickle-cell anemia are similar to those found in circulatory disturbances of bone. These are described as 1) degenerative processes (thrombosis, infarction, necrosis, hemorrhage) and 2) reparative processes (hyalinization, fibrosis, abnormal calcification, new bone formation). Smith[9] stated that in some cases of sickle-cell anemia the stage is already set for the occurrence of hematogenous osteomyelitis. He notes the similarity of the bone lesions of sickle-cell disease and the early lesions of acute hematogenous osteomyelitis (both show thrombosis and infarction), and suggests bacterial culture or agglutinations to differentiate sterile infarcts from localized infection in bone. Wigh and Thompson[4] have pointed out the presence of

cortical fissuring in osteomyelitis complicating sickle-cell anemia and they theorize that this may be due to underlying changes in compact bone due to the anemia. The process involves the diaphysis first and proceeds to produce distinctive lesions of the medullary portion, and periostitis.

In an analysis of 130 children with a proved diagnosis of osteomyelitis, Hughes and Carroll[13] showed a higher incidence in children with sickle-cell disease. There were only four Salmonella isolations, all in cases of sickle-cell anemia. The organism found in other cases of osteomyelitis in sicklers was hemolytic *Staphylococcus aureus*. They point out the marked disposition for multiple bone involvement in this syndrome and its occurrence chiefly in young children.

Roberts and Hilburg[16] found that of 885 cases of osteomyelitis three were caused by Salmonella. These 3 cases occurred in children with sickle-cell anemia. They postulated that the bone changes caused by sicklemia predispose to Salmonella osteomyelitis and that infection is caused by previously dormant medullary organisms or from transitory bacteremia. It is a known fact that living bacilli are found in bone marrow in cases of typhoid fever. Fraenkle, as quoted by Stenström,[20] felt that the bacilli may remain dormant in the bone marrow for decades.

It has been postulated that thrombosis in the gastrointestinal tract of sicklers predisposes to infection, while disease of the spleen may interfere with bodily defenses.[21]

While the most common types of Salmonella causing osteomyelitis in the general population are *S. paratyphi C*, *S. choleraesuis* and *S. typhimurium*,[17] almost all cases in sickle-cell anemia have been caused by the group B organisms, *S. paratyphi B* (*S. schottmülleri*) and *S. typhimurium*.

Salmonella infection without osteomyelitis has been reported to have caused an aplastic crisis in sicklemia.[22] A hemolytic anemia (probably toxic) has been reported in a 6 year old Arab girl with Salmonella osteomyelitis.[23] Another generalized disorder, lupus erythematosis, has been found associated with Salmonella osteomyelitis.[24]

TREATMENT

The treatment of salmonellosis is in general not very satisfactory. Rabe[25] tried five different antibiotic regimens for Salmonella gastroenteritis: 1) chloramphenicol (alone or with penicillin, streptomycin, chlortetracycline, oxytetracycline and sulfisoxazole); 2) penicillin and probenecid; 3) oxytetracycline and neomycin; 4) penicillin, probenecid and chloramphenicol; and 5) synnematin B[17]. Therapy eradicated the bacteria from the gastrointestinal tract in 32 per cent of the treated cases. It was found that no single method was superior to any other method studied. Since he was unable to find a published series to determine whether or not the 32 per

cent incidence of negative rectal cultures found one month after completion of therapy is better or worse than no treatment at all, he was unable to determine the absolute success of his efforts.

Saphra[26], in a series of several hundred Salmonella cases, found chloramphenicol most consistently active; other antibiotics shown to be of some use were dihydrostreptomycin and tetracycline. He recommends that no antibiotic be used in simple Salmonella gastroenteritis and states:

> It should be stressed that, in contrast to favorable reports of successful treatment in Salmonella gastroenteritis, there is no evidence that the use of antibiotics over days and weeks helps in terminating more effectively a diarrhea, and particularly a carrier state. A prolonged and massive treatment with broad-spectrum antibiotics severely upsets the bacterial balance in the intestines, frequently leads to overgrowth of Monilia, staphylococci, Pseudomonas, and Proteus, and at best temporarily inhibits the pathogens that frequently reappear a few days after the discontinuation of the antibiotics.

He feels that the use of antibiotics is not indicated in simple gastroenteritis, but when the infection is generalized he prefers the use of parenteral chloramphenicol.

The use of typhoid-paratyphoid vaccine in the therapy of salmonellosis has shown promise, especially in reducing the rate of relapse.[27]

Since osteomyelitis developing in sickle-cell disease is caused predominantly by either Salmonella or *Micrococcus pyogenes var. aureus*, Hughes and Carroll[13] suggest the combined use of chloramphenicol and erythromycin while awaiting results of cultures in sicklers who develop bone infection.

SUMMARY

The more than coincident occurrence of Salmonella osteomyelitis in sickle-cell anemia is discussed and a case reported. The underlying bone pathology in sicklemia is believed to make these individuals more susceptible to osteomyelitis than normal persons. The treatment of salmonellosis is briefly discussed.

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The Editor's Column

Immunization Practices in Bleeding Disorders

A problem which must be considered by pediatricians and hematologists alike is the prophylactic immunization of infants and children with bleeding disorders. The issue at hand is the possibility of producing hemorrhage by such procedures versus the dangers of allowing these patients to remain susceptible to such diseases as pertussis, diphtheria, tetanus or poliomyelitis.

In order to establish a definite policy concerning this question a survey of the opinions of a group of pediatric hematologists from various centers was recently conducted by this author. The questions which were submitted to these individuals were "Would you give prophylactic injections and vaccinations to infants and children with bleeding and clotting disorders such as thrombocytopenic purpura and hemophilia?", and if the first answer was in the affirmative, "Would you take any specific precaution?"

Although there were some divergences on minor points, on the whole there was unanimity of opinion on the major issues.

Because thrombocytopenic purpura is a relatively short-lived and self-limited disease it was felt that one could defer immunization until recovery has occurred. In the case of the patient with chronic thrombocytopenia, if the hemorrhage manifestation were not too severe, most participants felt that intramuscular injections of toxoid would be well tolerated.

In the case of the hemophiliac syndrome there was strong agreement that immunization should be given, since the child with these hemorrhagic disorders is in far greater danger from infectious diseases than from the injection itself. Surprisingly, and in accord with this author's experience, severe hematomas were not often observed following the intramuscular injection of triple toxoid or poliomyelitis vaccine, or after vaccination.

Several valuable suggestions were made concerning immunization in the hemophiliac child. It was suggested that these procedures be limited to a time when signs of hemorrhage are not present. The deltoid or gluteal regions were considered equally satisfactory sites for intramuscular injections; a relatively small needle was recommended. The intracutaneous route was employed with success by one hematologist who gave triple toxoid in doses of 0.2 ml. once a month for three months, and a booster dose at five to six months.

It was not considered necessary to prepare the patient with plasma infusions prior to these injections because of the infrequency of reported sequelae. However, if intramuscular bleeding did occur, fresh plasma was given intravenously as soon as possible.

It would appear from the response of these clinicians that the slight

danger of hemorrhage in the hemophiliac patient is tremendously outweighed by the advantage of the prevention of these potentially complicating diseases.

S. L.

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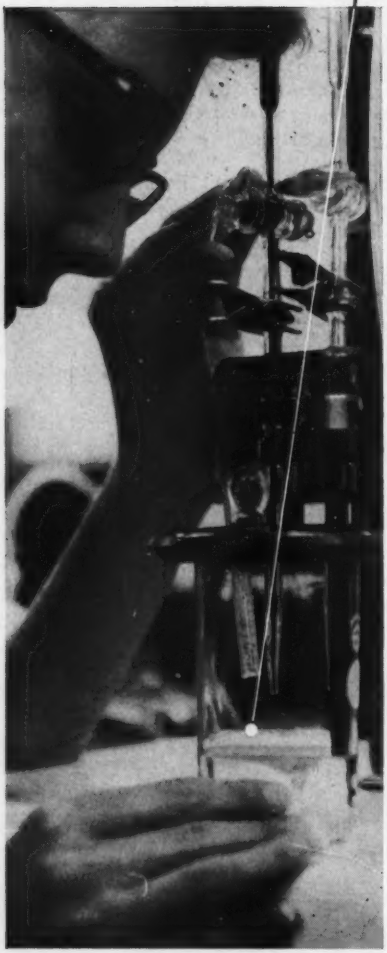

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